Trial designs to measure population impact of interventions

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## Interventions proven to prevent acquisition of HIV

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>Effectiveness</th>
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<tbody>
<tr>
<td>ARV in pregnancy and delivery; ARV in infant during breastfeeding</td>
<td>Infants</td>
<td>30%-98%</td>
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<tr>
<td>Male Circumcision</td>
<td>Heterosexual men</td>
<td>50%-60%</td>
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<tr>
<td>ARV-based microbicide in South Africa</td>
<td>Heterosexual women</td>
<td>39%</td>
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<tr>
<td>Oral pre-exposure prophylaxis use of Truvada</td>
<td>MSM</td>
<td>44%</td>
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<tr>
<td>Early vs. delayed treatment with ART</td>
<td>Heterosexual men and women</td>
<td>96%</td>
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“Combination Prevention”

• Multi-component intervention

  For example

  • Annual HIV testing
  • Enhanced linkage to care for HIV+
  • Early initiation of ART for HIV-infected
  • Adherence intervention
  • Circumcision for HIV-uninfected men
What to compare? Heated debate over combination prevention designs

**Combination - “Kitchen sink”**
- Universal ART and Mobile Male Circumcision
  - ARM 1: MC+, ART+
  - ARM 2: MC-, ART-
- MC SoC + ART by National Guidelines

**Factorial - “One at a time”**
- Universal ART
- ART by National Guidelines
- Mobile Male Circumcision by Standard of Care
  - ARM 1: MC+, ART+
  - ARM 2: MC+ ART-
  - ARM 3: MC-, ART+
  - ARM 4: MC-, ART-
Trials measuring population level impact of intervention scale-up

- Address the “responsibility gap”
  - Proven efficacy
  - Scale-up to impact the epidemic
- What study designs are appropriate?
- What endpoints do we use?
- What is the added-value of assessing the population impact with HIV seroincidence?
Assessing population impact

- Mathematical modeling
  - Extrapolate from existing data

- Observational study design
  - Epidemiologic population observation
  - Pre- vs. post- measurement of population

- Randomized designs
  - Parallel community randomized trial
  - Step-wedge community randomized trial
Observational Designs

- Serial cohorts
  - Pre-Intervention Incidence Rate
  - Intervention(s)
  - Post-Intervention Incidence Rate

- Long-term cohort
  - Long-term Cohort
  - Intervention(s)
  - Trend in Incidence Rate

- HIV testing
Pros and Cons of Observational Design

• Advantage: Move directly to implementation
• Disadvantage:
  – No protection against epidemiologic trends
  – No replication
Community Randomized Designs

- Parallel randomization

Randomize:
- Arm 1: Community 1
- Arm 1: Community 2
- Arm 1: Community 3
- Arm 1: Community...
- Arm 2: Community 5
- Arm 2: Community 6
- Arm 2: Community 7
- Arm 2: Community ...

Intervention → Measure
Community Randomized Designs

- “Step-wedge” randomization

Randomize 6 communities

- Arm 1
- Arm 1
- Arm 1
- Arm 1
- Arm 1
- Arm 1

Measure

Result
Pros and Cons of Community Randomized designs

- Advantage: A randomized comparison
- Disadvantage:
  - No implementation in some communities
  - Contamination risk
    - Intervention contamination
    - Migration/mixing of communities

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<thead>
<tr>
<th></th>
<th>Parallel Randomized</th>
<th>Step Randomized</th>
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<tbody>
<tr>
<td>Advantages</td>
<td>Simple design</td>
<td>Assess effect with implementation in few communities at a time</td>
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</tbody>
</table>
| Disadvantages          | Simultaneous implementation in multiple communities | • Requires rapid effect on outcome  
                        |                                            | • More complex analysis                        |
What to measure?  
Who to measure?  
How to measure?

- **Coverage**: How many people in the target population were reached?
  - Population based survey: self report, physical exam, lab assessments
  - Monitoring and evaluation of services delivered: medical records; clinic based data collection

- **HIV seroincidence**: What was the change in seroincidence?
  - Population-based sample or subgroup sample with longitudinal follow-up
  - Cross-sectional sample: Assay for recent infection
Do we need to measure population impact with HIV seroincidence?

Pros

- Necessary when combining interventions of modest or unproven effectiveness
- For proven interventions, efficacy benefits from individual RCT do not easily translate to population effects: indirect effects unknown
- Data on cost-effectiveness
- Impact on public perception

Cons

- Size, complexity, cost and time
- Coverage sufficient for direct effects
- If HIV incidence doesn’t change, what do we learn?
  - Coverage inadequate
  - Epidemiologic trends (Observation design)
  - Contamination between communities (Community Randomized)
Swaziland Accelerated Saturation Initiative “Soka Unkobe”

- Goal: From 8% to 80% of HIV-uninfected adult males circumcised in one year
- In addition, prevention due to:
  - HIV testing in males
  - Linkage to care
  - Increased access to ART at CD4<350
- PEPFAR funding for implementation
HIV testing

31,749 cohort participants over 3½ yrs total

Men and Women 18-49 years
A1 Sample Size = 5823 M / 6634 W
A2 Sample Size = 6165 M / 9877 W

Pre-Campaign Incidence Rate

A1 [12, 357]

Post-Campaign Incidence Rate

A2 [16,042]

Pre-/Post- Incidence Reduction

Prevention Campaign

- Male Circumcision
- ART referral

12 mos

0 6 18 30 36 42 48

2011 → 2014

Swaziland HIV Incidence Study

Swaziland HIV Incidence Study
Measuring community-level seroincidence

Representative sample of community:
- Household based sampling
- Multi-stage sampling
  - e.g. Evaluation area, Household, Person
  - Design effect (increase in variance of outcome as result of sampling scheme)
- Weighted analysis
  - Non-response bias
  - Design effect
Challenges

- Defining communities matched to intervention
- Minimize contamination risk
  - Contamination of intervention
  - Sexual mixing patterns
  - Migration
- Sufficient communities to randomize
- Delays in scale-up, delays in effect
- Achieving balance in randomization
The Scientific Method

Here are the facts. What conclusions can we draw from them?

The Creationist Method

Here’s the conclusion. What facts can we find to support it?
Summary

• Changing the course of the HIV epidemic will likely need effective interventions with high population coverage.

• Population impact trials will be expensive and difficult, but ultimately most persuasive.

• Will require our utmost:
  – Commitment of sponsors, implementers, investigators
  – Engagement of community
  – Critical thinking and analysis
  – Multidisciplinary approach